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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Sadat-Aalaee et al.		
Serial No.:	09/980,943	ART UNIT:	1654
Filed:	February 22, 2002	EXAMINER:	Russel, Jeffrey
Entitled:	SOMATOSTATIN AGONISTS		

Attorney Docket No.: BIO-093.1P US

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DECLARATION OF John E. Taylor
UNDER 37 C.F.R. §1.132

I, John E. Taylor, hereby declare and state that:

1. I am familiar with the subject matter claimed in the above-identified patent application, U.S. Serial No. 09/980,943.

2. I have a Ph.D. in Pharmacology and I serve as Associate Director of Receptor and Cellular Biology at Biomeasure, Incorporated.

3. I understand that the last office action issued in this application was dated May 16, 2003 and that the Examiner of this application is of the view and stated in the office action that in the absence of data supporting the claimed agonist activity of the compounds of the present invention, the Examiner contends that the compounds are prima facie obvious over the antagonist compounds disclosed in international application PCT/US97/22251 (WO 98/24807).

4. I make this declaration to show that data generated by following the procedures disclosed and discussed in the application provide sufficient and convincing evidence that the compounds of the present invention are specific for somatostatin receptors as well as possess the ability to evoke a somatostatin-like response from cells expressing a

somatostatin receptor. One of skill in the art would readily appreciate that the efficacy of any of the compounds of the invention can be determined by using such standard assays. Thus, a person of skilled in the art would have be able to determine the suitability of the compounds of Claim 1 for the claimed methods of use.

5. As disclosed in the specification on page 2, lines 14-16, the peptides of the present invention are a previously unknown sub-genus encompassed by the larger group of compounds disclosed in U.S. Application No. 08/855,204, which has now issued as U.S. Patent No. 6,262,229. Like the compounds of the '229 patent, the compounds of the present invention, i.e., compounds of formula (I) (Claim 1), possess high affinity for somatostatin receptors. Unlike the compounds of the '204 application, however, the compounds of the present invention were discovered to possess agonist activity.

6. Regarding somatostatin receptor affinity, the application discloses details of an assay known in the art* for determining a compound's affinity for somatostatin receptors. See page 11 (line 2) through page 13 (line 11). Using this assay, I have determined the inhibition constants (Ki) for the five human somatostatin receptors (hSSTR1 - hSSTR5) for representative compounds of the invention, as follows:

Cpa–cyclo(DCys–3–Pal–DTrp–Lys–Ala–Cys)–Nal–NH_2 (Example 1 in the specification):

hSSTR1	hSSTR2	hSSTR3	hSSTR4	hSSTR5
529 (nM)	444 (nM)	247 (nM)	1000 (nM)	159 (nM)

Cpa–cyclo(DCys–3–Pal–DTrp–Lys–Gaba–Cys)–Nal–NH_2 (Example 2 in the specification):

hSSTR1	hSSTR2	hSSTR3	hSSTR4	hSSTR5
1000 (nM)	327 (nM)	519 (nM)	1000 (nM)	13.4 (nM)

7. The data above show the relative specificity of the invention compounds for the human somatostatin receptors, in particular somatostatin receptor 5. Additional members of the formula (I) family of compounds are taught to have similar specificity for somatostatin receptor(s), which specificity can be readily confirmed employing the above-described standard assay.

* See, e.g., U.S. Patent No. 5,972,893, example 7 therein.

8. Regarding somatostatin agonist activity, it is well appreciated in the art that there are a number of assays which are useful for determining whether a compound possesses agonist or antagonist properties. One such assay is disclosed in the instant application at page 13, lines 12-30. Another commonly employed assay is microphysiometry. Microphysiometry is an *in vitro* bioassay based on real-time quantitation of receptor-activated metabolic rate changes, e.g., relative to a known ligand for the receptor. This technique has been well known in the art for some time (microphysiometers are commercially available). Details of the procedure used to evaluate the compounds of Example 1 and Example 2 in the specification are recited below:

> Cultured CHO-K1 cells expressing the hSSTR2 receptor were seeded onto 12 mm capsule cups (Molecular Devices, Corp.) in Dublecco's modified Eagle's Medium (DMEM) containing 10% fetal bovine serum at a density of 10^6 cells/well, and maintained in culture (5% CO_2, 37°C, humidified air) for 24 hours prior to use. The cell capsules were installed into the Cytosensor Microphysiometer (Molecular Devices Corp.), perfused (100 µl/min), and equilibrated with bicarbonate-free DMEM containing 1.0 mM sodium phosphate and 1 mg/ml bovine serum albumin (BSA), for approximately three hours. The cells were exposed to the somatostatin peptides for 120 seconds and the metabolic rate measurement (acidification rate) was determined during a pause in cell perfusion during the last 30 seconds of the peptide exposure cycle.

Results:

Somatostatin-14 (100 nM):	100% activation (control)
Example 1 (100 nM):	29% activation (agonist)
Example 2 (100 nM):	25% activation (agonist)

9. The foregoing experiments confirm the teaching of the application, namely, the specificity of compounds of the invention for somatostatin receptors as well as their ability to evoke a somatostatin-like response from cells expressing a somatostatin receptor, i.e., somatostatin agonist activity. The various alternative compound substituents provided for in Claim 1 were selected because they are expected to maintain similar specificity and agonist activity as the above examples.

10. Based on the results using known techniques, others skilled in the art would readily appreciate that the efficacy of any of the compounds of the invention can be confirmed quite simply by using the standard assays referenced in the application. Thus, the

application supplies sufficient data and information to practice the invention of the claims. In view of the data presented above and the Applicants' comments, it is believed that the Examiner's concern has been addressed.

10. I further declare that all statements made herein of my own knowledge are true and that statements made upon information and belief are believed to be true and further that false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

10/3/03
date

DECLARANT